IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1616
Yerramilli V.S.N. Murthy and Robert H. Suva	Examiner: K. George
Serial No.: 10/274,445	Atty. Docket: 051091-0302
Filed: October 18, 2002	
For: INJECTABLE COMPOSITION FOR THE CONTROLLED DELIVERY OF PHARMACOLOGICALLY ACTIVE COMPOUND	

DECLARATION UNDER 37 C.F.R. 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

1. I, Yerramilli V.S.N. Murthy, am a research scientist for IDEXX Laboratories, Inc. and a co-inventor of U.S. Patent Application Ser. No. 10/274,445. I have a Ph.D. in Chemistry and have worked in the field of chemistry for 13 years.

2. I have been informed that U.S. Patent No. 5,574,020 entitled "Tilmicosin Formulations" by Klink et al. has been cited against the application as allegedly anticipating the claimed invention. I have reviewed and understand the disclosure set forth in this patent.

3. I have made various tilmicosin formulations following the teachings in Klink et al.[1]

Klink et al Formulations (Declaration Paragraphs 4-16)

4. For the formulations shown in attached Exhibits A (left photo) and B, the following procedure was followed to create 100 ml batches (30% tilmicosin; 25% propylene glycol) at room temperature:

[1] Klink et al. Abstract: "An aqueous, sustained release tilmicosin formulation comprises 250-350 mg/ml of tilmicosin and 250 mg/ml of propylene glycol, and has a pH adjusted to 6.". "The preferred concentration of tilmicosin is 300 mg/ml." C1:L43 (i.e. 30 % tilmicosin by weight). Propylene glycol ranges from 200 mg/ml to 414 mg/ml (see: Abstract; Cl:L40; C1:L64 to C2:L11; and Test Data in C2).

- 32.94 g of tilmicosin (91.1% pure)[2] was slurried in 36 ml of deionized water;
- with stirring, acid was added to adjust the pH to 6 – a clear solution was obtained in about 30 minutes;
- 25 ml propylene glycol (about 25%[3]) was added and mixed well;
- volume was adjusted to 100 ml with water[4]; and
- the resulting mixture was stirred for 1 hour and then photographed.

5. Exhibit A (left photo) shows 50 ml of the above Klink et al. formulation using phosphoric acid. Upon visual inspection, this formulation was clear, homogeneous and had no precipitates. The formulation could be drawn into a syringe. 3 ml of this formulation was drawn into a syringe and injected into a second beaker containing 50 ml deionized water at room temperature. The injected formulation did not precipitate (see Exhibit A, right photo).

6. Exhibit B shows 100 ml of the above Klink et al. formulation using hydrochloric acid. Upon visual inspection, this formulation was clear, homogeneous and had no precipitates. The formulation could be drawn into a syringe. The formulation did not precipitate when injected into water (not shown).

7. For the formulation shown in attached Exhibit C1 (lauric acid), the following procedure was followed in an attempt to formulate a 100 ml batch (30% tilmicosin; 25% propylene glycol) at room temperature:

- 32.94 g of tilmicosin (91.1% pure) was slurried in 36 ml of deionized water;
- with stirring, 14.5 g lauric acid was added to the slurry[5];
- after 30 minutes, 25 ml propylene glycol (25%) was added; and
- the resulting highly viscous mixture was stirred for 1 hour and then photographed.

8. The lauric acid formulation in Exhibit C1 had significant amounts of gummy precipitates. The formulation could not be drawn into a syringe. The pH of the formulation was about 7.

9. Further addition of 20.71 g lauric acid to a total amount of 5 equivalents (relative to tilmicosin) was added with stirring to the Exhibit C1 formulation, shown in Exhibit C2. The lauric acid formulation in Exhibit C2 had significant amounts of gummy precipitates. The formulation could not be drawn into a syringe. The pH of the formulation remained at about 7,

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[2] 32.94 x 0.911 = 30.00 grams of tilmicosin

[3] The specific gravity of propylene glycol is about 1.035-1.037; 25 ml propylene glycol in 100 ml total is about 25% propylene glycol.

[4] 30 g of tilmicosin in 100 ml of liquid equals 300 mg/ml tilmicosin.

[5] Tilmicosin has two basic sites (amine groups) - formulations made with 2.1 equivalents of acid result in neutralized tilmicosin. 14.5 g lauric acid equals 2.1 equivalents relative to tilmicosin.

i.e. the further addition of lauric acid failed to lower the pH.

10. For the formulation shown in attached Exhibit D1 (lauric acid), the following procedure was followed in an attempt to formulate a 100 ml batch (30% tilmicosin; 41.4% propylene glycol) at room temperature:

- 32.94 g of tilmicosin (91.1% pure) was slurried in 25 ml of deionized water;
- with stirring, 14.5 g lauric acid was added to the slurry;
- after 30 minutes, 41.4 ml propylene glycol (41.4%) was added; and
- the resulting highly viscous mixture was stirred for 3 hours and then photographed.

11. The lauric acid formulation in Exhibit D1 had significant amounts of gummy precipitates. The formulation could not be drawn into a syringe. The pH of the formulation was about 7.

12. Further addition of 20.71 g lauric acid to a total amount of 5 equivalents (relative to tilmicosin) was added with stirring to the Exhibit D1 formulation, shown in Exhibit D2. The lauric acid formulation in Exhibit D2 had significant amounts of gummy precipitates. The formulation could not be drawn into a syringe. The pH of the formulation remained at about 7, i.e. the further addition of lauric acid failed to lower the pH.

13. For the formulations shown in attached Exhibits E, F and G, the following procedure was followed in an attempt to formulate a 100 ml batches (25% tilmicosin; 25% propylene glycol) at room temperature:

- 27.45 g of tilmicosin (91.1% pure) was slurried in 36 ml of deionized water;
- with stirring, acid was added in the amount of 2.1 equivalents to tilmicosin;
- after 30 minutes, 25 ml propylene glycol (25%) was added;
- the resulting mixture was stirred for 3 hours and then photographed.

14. Exhibit E shows a formulation using palmitic acid. This formulation had significant amounts of gummy precipitates. The formulation could not be drawn into a syringe.

15. Exhibit F1 shows a formulation using pamoic acid. This formulation had significant amounts of gummy precipitates that remained in the beaker upon inversion (Exhibit F2). The formulation could not be drawn into a syringe.

16. Exhibit G1 shows a formulation using stearic acid. This formulation had significant amounts of gummy precipitates that remained in the beaker upon inversion (Exhibit G2). The formulation could not be drawn into a syringe.

Examples of the Present Invention using Tilmicosin (Declaration Paragraphs 17-22) [6]

Declaration Example 1 – 30% Tilmicosin:Lauric Acid in N-methyl Pyrrolidone

17. The following procedure was followed to formulate a 100 ml batch of 30% tilmicosin:lauric acid in N-methyl Pyrrolidone (NMP) at room temperature (i.e. 300 mg/ml tilmicosin):

- 32.94 g of tilmicosin (91.1% pure) was mixed with 36 ml of NMP;
- with stirring, 14.5 g lauric acid was added and mixed well to obtain a clear solution; and
- volume was adjusted to 100 ml with NMP.

18. 50 ml of this Declaration Example 1 formulation was transferred to a 100 ml beaker (Exhibit H, left photo). 3 ml of this formulation was drawn into a syringe and injected into a second beaker containing 50 ml deionized water at room temperature. Precipitates formed, resulting in a turbid solution (Exhibit H, right photo).

Declaration Example 2 – 30% Tilmicosin:Lauric Acid in 10% Propylene Glycol in Glycerol Formal

19. The following procedure was followed to formulate a 100 ml batch of 30% tilmicosin:lauric acid in 10% propylene glycol in glycerol formal at room temperature (i.e. 300 mg/ml tilmicosin):

- 32.94 g of tilmicosin (91.1% pure) was mixed with 36 ml glycerol formal and 10 ml propylene glycol;
- with stirring, 14.5 g lauric acid was added and mixed well to obtain a clear solution; and
- volume was adjusted to 100 ml with glycerol formal.

20. 50 ml of this Declaration Example 2 formulation was transferred to a 100 ml beaker (Exhibit I, left photo). 3 ml of this formulation was drawn into a syringe and injected into a second beaker containing 50 ml deionized water at room temperature. Precipitates formed, resulting in a turbid solution (Exhibit I, right photo).

Declaration Example 3 – 10% Tilmicosin:Lauric Acid in 10% Propylene Glycol in Glycerol Formal

21. The following procedure was followed to formulate a 100 ml batch of 10% tilmicosin:lauric acid in 10% propylene glycol in glycerol formal at room temperature (i.e. 100

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[6] The present specification as filed (US Serial No. 10/274,445) has several specific examples using tilmicosin as the active ingredient (see pages 15-20). Such examples used between 100 and 600 mg/ml tilmicosin (i.e. between 10 and 60 g tilmicosin in 100 ml batches) using various solvents, including N-methyl Pyrrolidone (NMP) and 10% propylene glycol in glycerol formal. Lauric acid is also disclosed as a source of lipohilic conterions.

mg/ml tilmicosin):

- 10.98 g of tilmicosin (91.1% pure) was mixed with 36 ml glycerol formal and 10 ml propylene glycol;
- with stirring, 4.83 g lauric acid was added and mixed well to obtain a clear solution; and
- volume was adjusted to 100 ml with glycerol formal.

22. 50 ml of this Declaration Example 3 formulation was transferred to a 100 ml beaker (Exhibit J, left photo). 3 ml of this formulation was drawn into a syringe and injected into a second beaker containing 50 ml deionized water at room temperature. Precipitates formed, resulting in a turbid solution (Exhibit J, right photo).

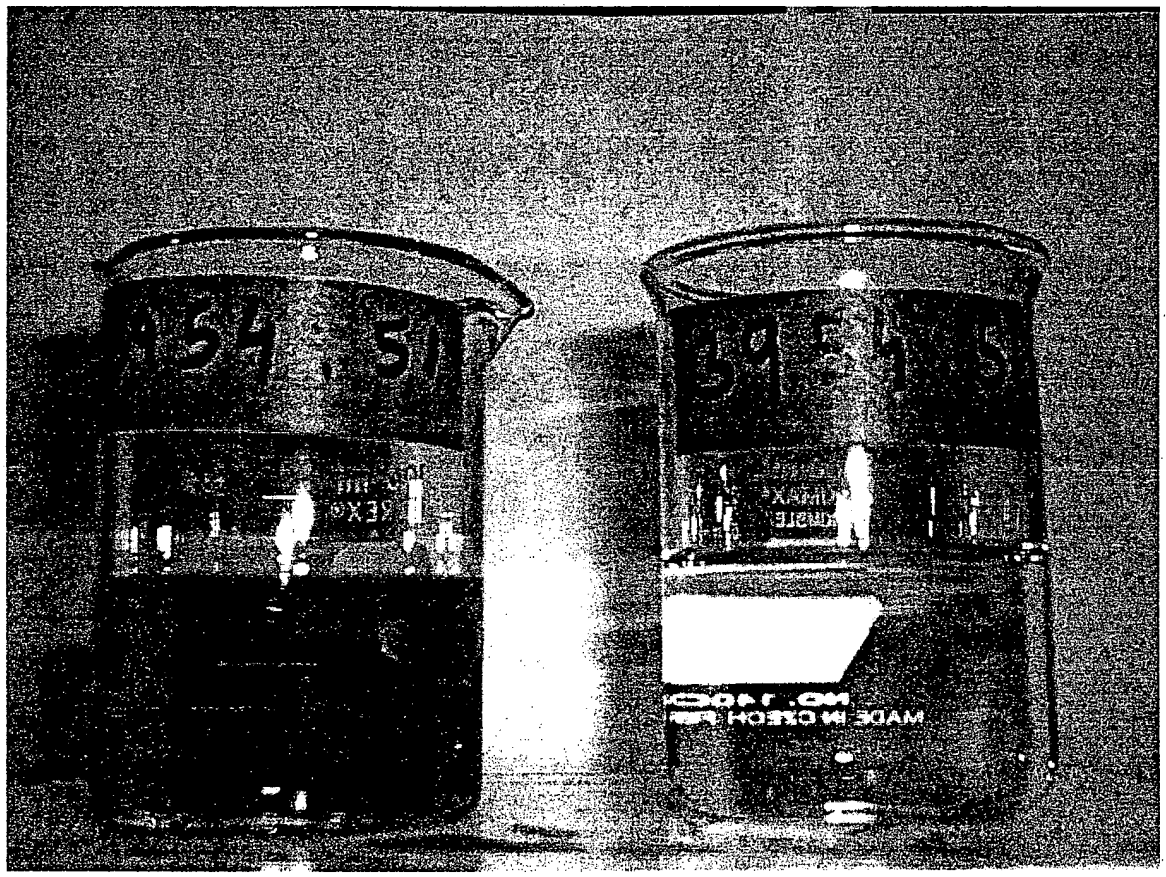
23. I hereby certify that all statement made herein of my own knowledge are true and that all statement made on information and belief are believed to be true; and further that these statement were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United sates Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 07/26/04

By: VSN Murthy
Yerramilli V.S.N. Murthy

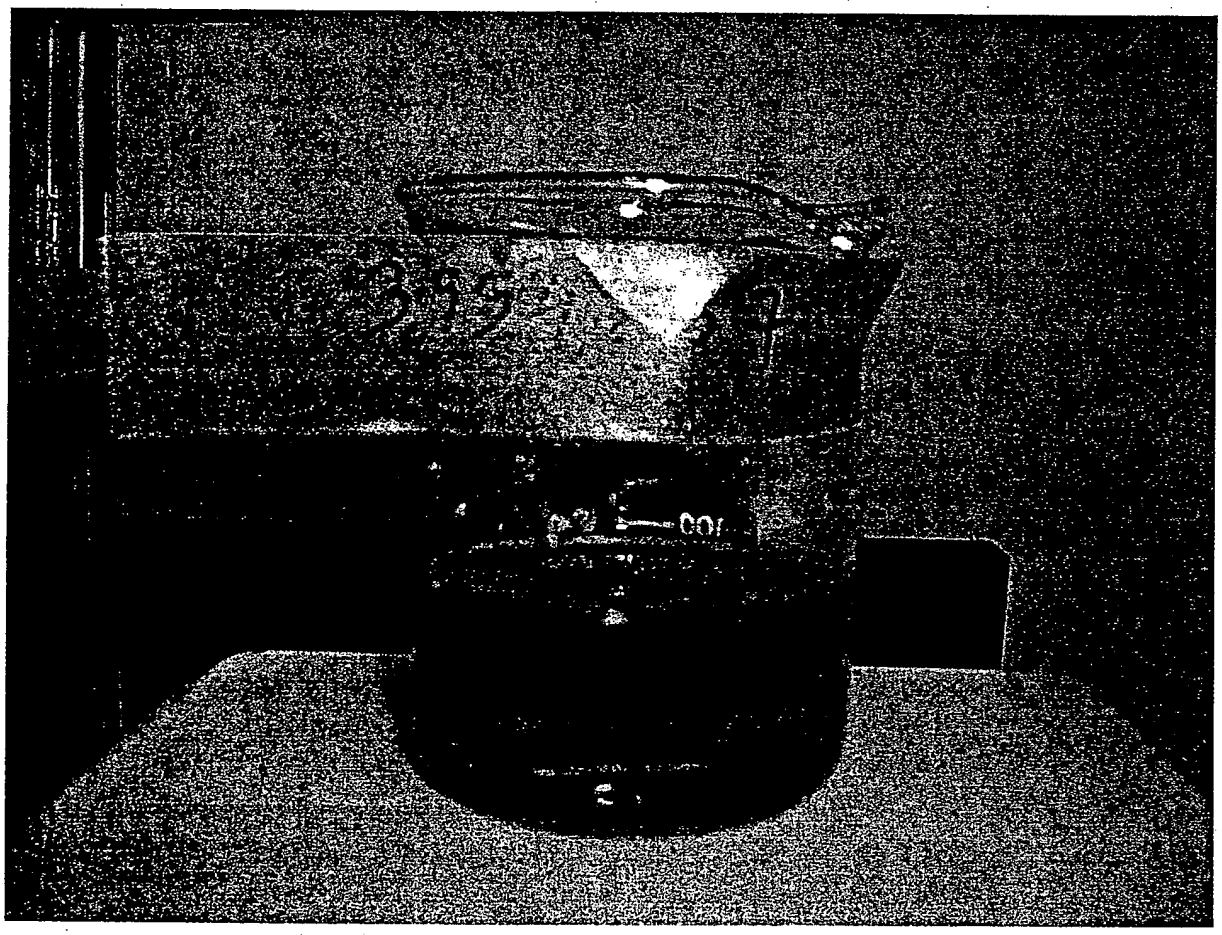
Murthy Exhibit A

Klink et al. Formulation
30% Tilmicosin - Phosphoric Acid (left)
3 ml of the 3954:51 formulation after injection into 50 ml water (right)



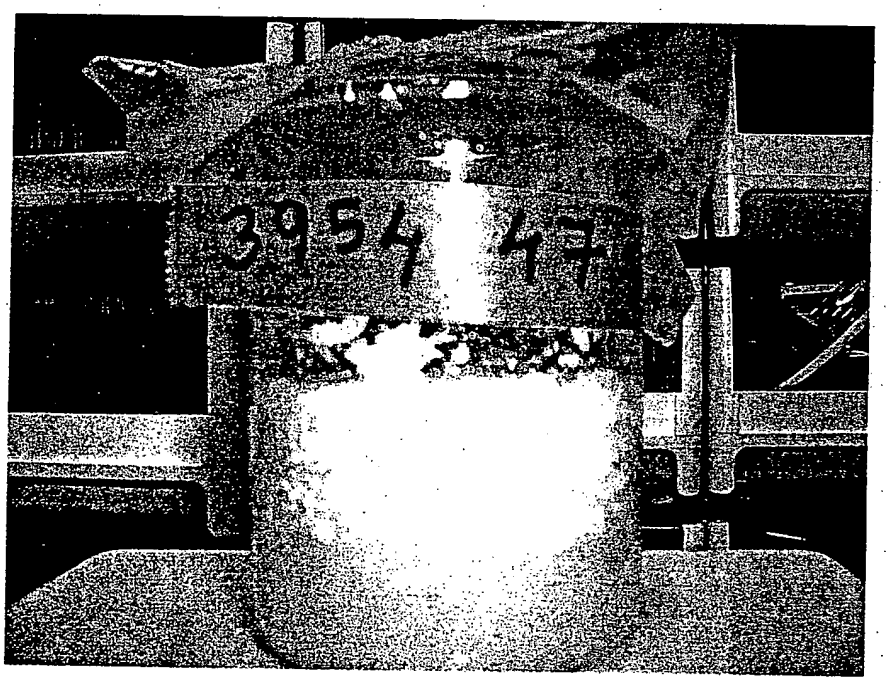
Murthy Exhibit B

Klink et al. – Hydrochloric Acid

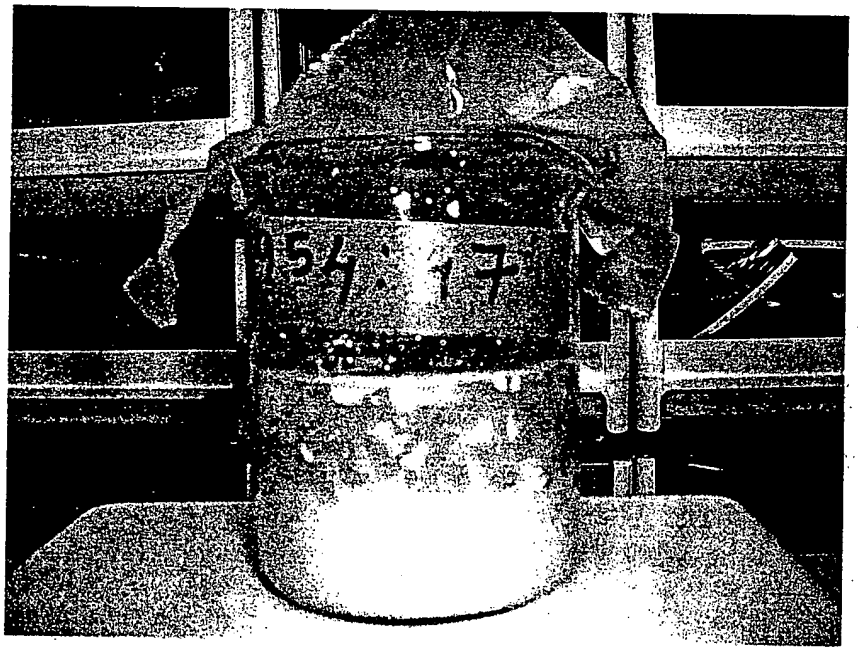


Murthy Exhibits C1 and C2

Klink et al. – Lauric Acid (30% Tilmicosin; 25% Propylene Glycol)



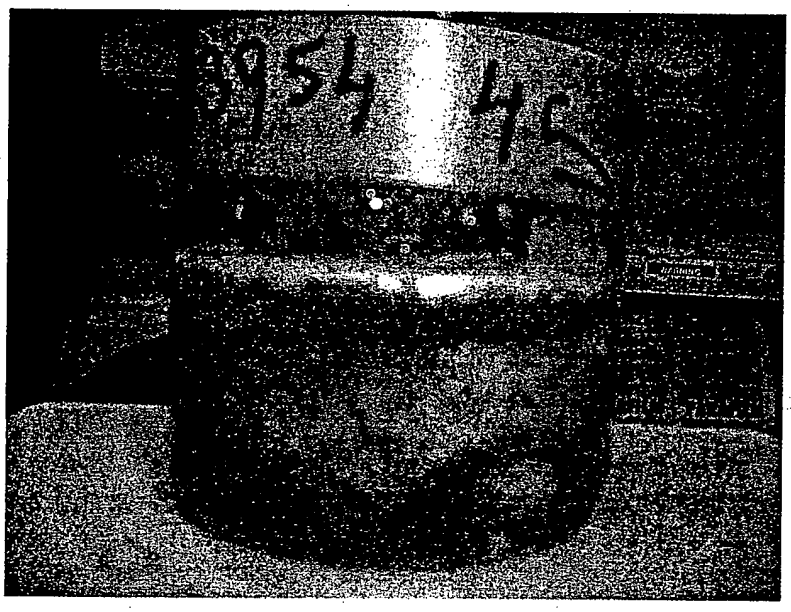
C1: 2.1 Equivalents Lauric Acid



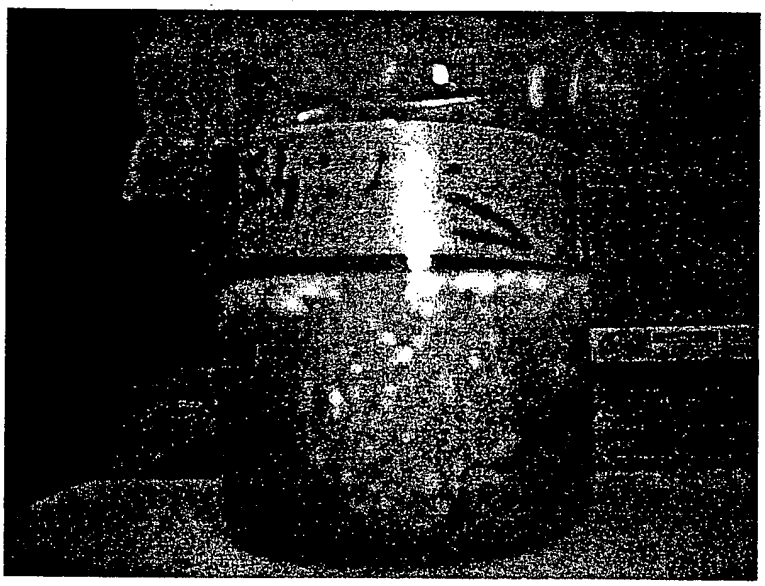
C2: 5 Equivalents Lauric Acid

Murthy Exhibits D1 and D2

Klink et al. – Lauric Acid (30% Tilmicosin; 41.4% Propylene Glycol)



D1: 2.1 Equivalents Lauric Acid



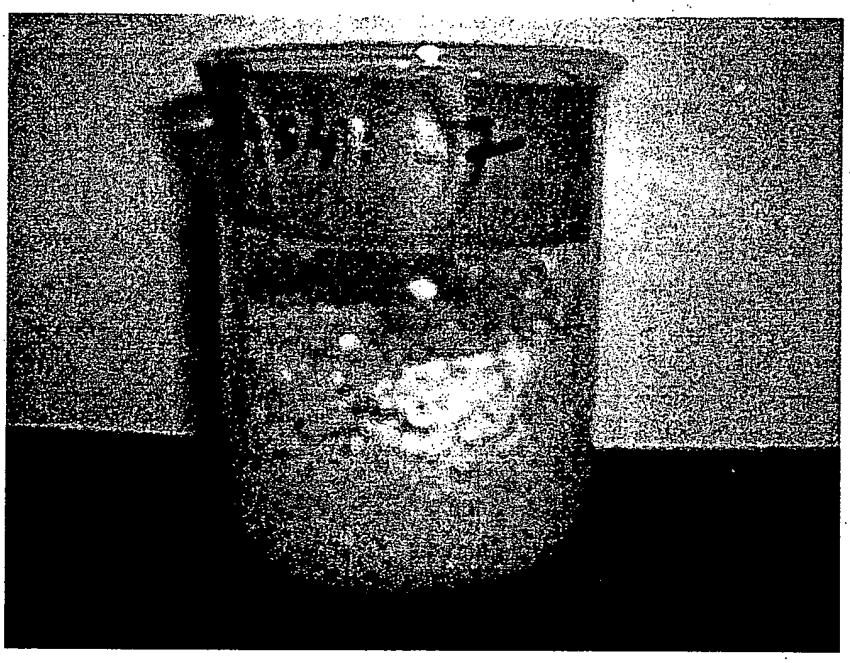
D2: 5 Equivalents Lauric Acid

Murthy Exhibit E

Klink et al. – Palmitic Acid

Murthy Exhibit F1 and F2

Klink et al. – Pamoic Acid



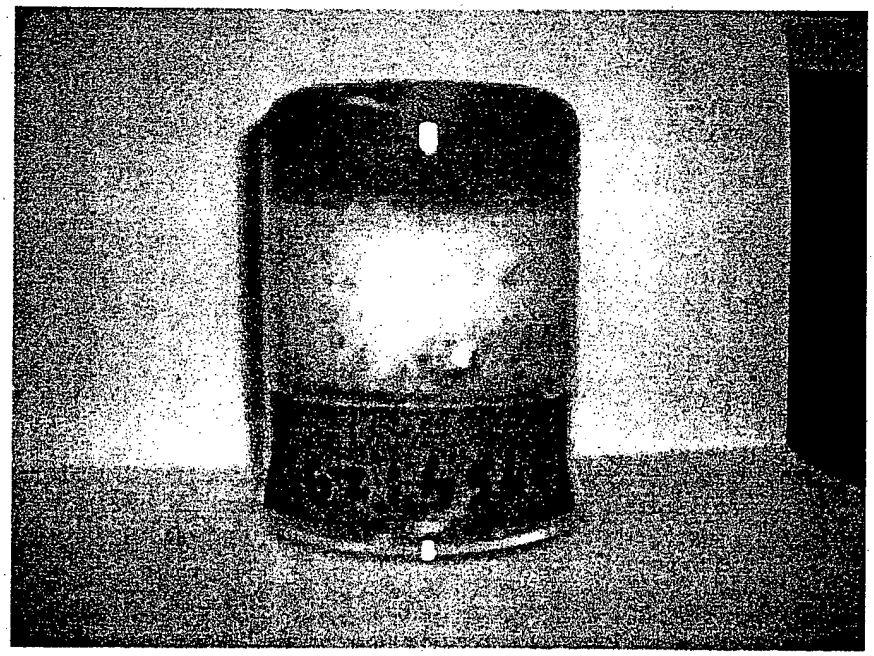
F1

F2

Murthy Exhibit G1 and G2

Klink et al. – Stearic Acid

G1



G2

Murthy Exhibit H

Murthy et al. Formulation (relating to the present invention)
30% Tilmicosin – Lauric Acid in N-methyl Pyrrolidone (left)
3 ml of the 3954:53 formulation after injection into 50 ml water (right)

Murthy Exhibit I

Murthy et al. Formulation (relating to the present invention)
30% Tilmicosin – Lauric Acid in 10% Propylene Glycol:90% Glycerol Formal (left)
3 ml of the 3954:55 formulation after injection into 50 ml water (right)

Murthy Exhibit J

Murthy et al. Formulation (relating to the present invention)
10% Tilmicosin – Lauric Acid in 10% Propylene Glycol:90% Glycerol Formal (left)
3 ml of the 3954:75 formulation after injection into 50 ml water (right)

Murthy Exhibit A

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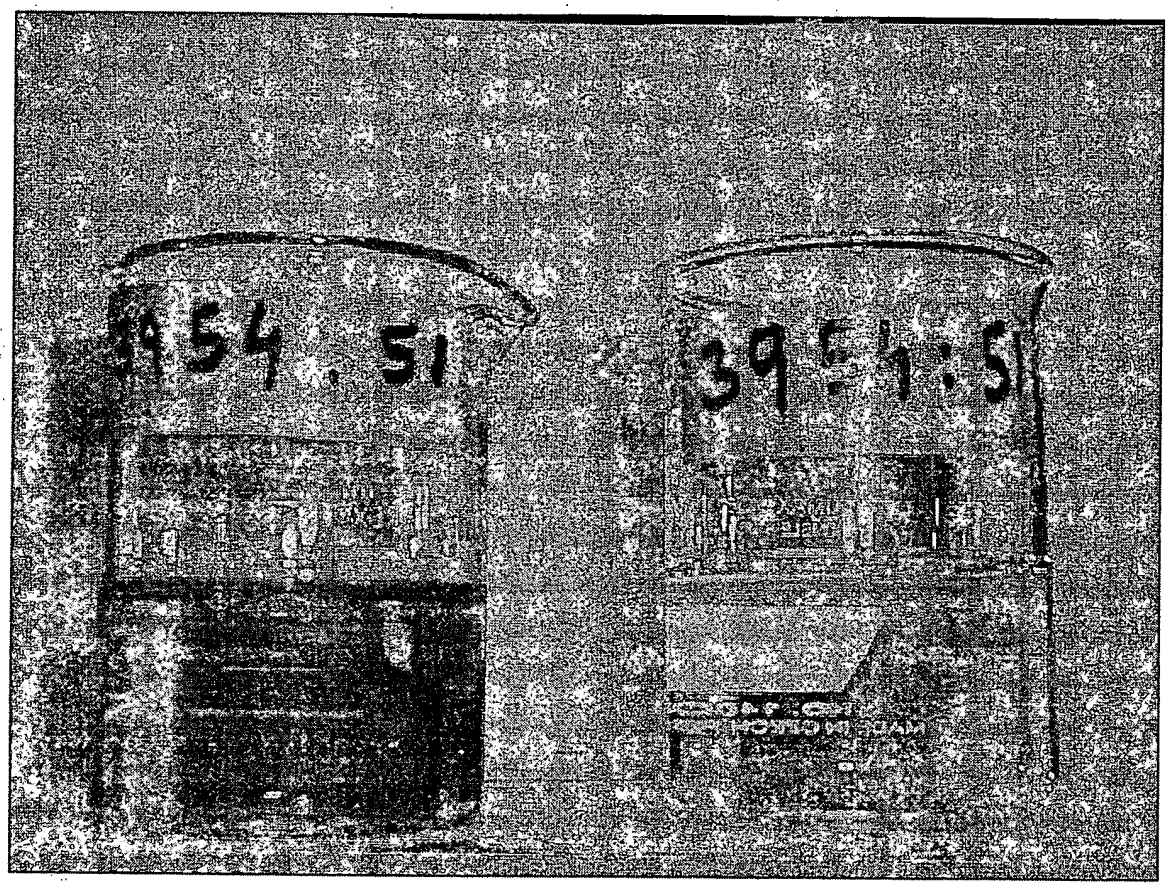
30% Tilmicosin - Phosphoric Acid (left)
3 ml of the 3954:51 formulation after injection into 50 ml water (right)



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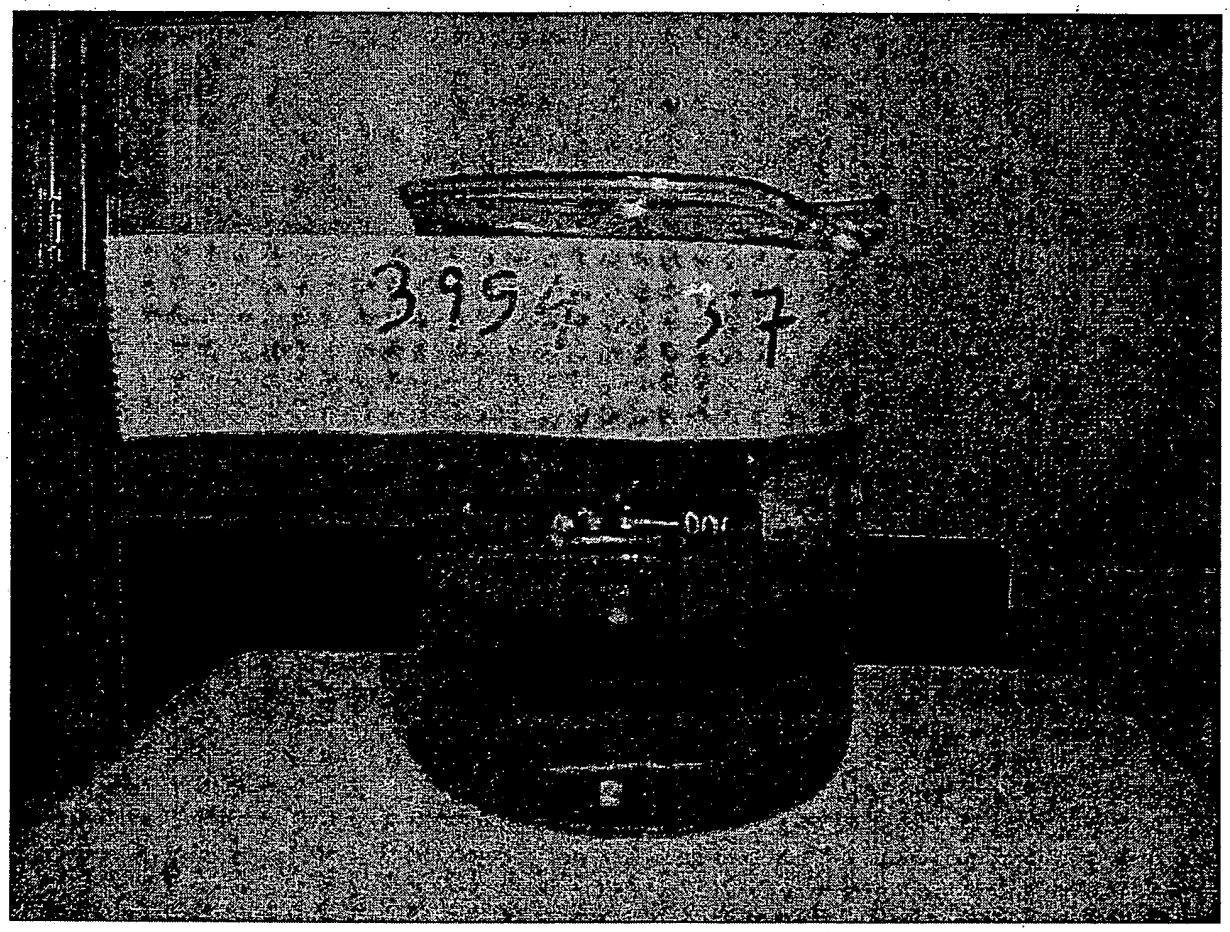
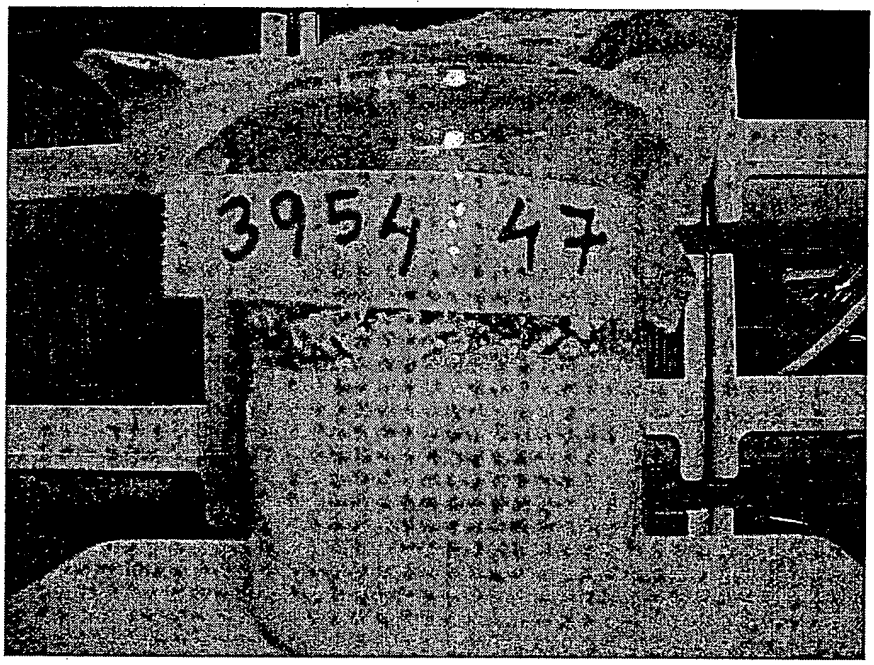


Murthy Exhibits C1 and C2

Klink et al. – Lauric Acid (30% Tilmicosin; 25% Propylene Glycol)



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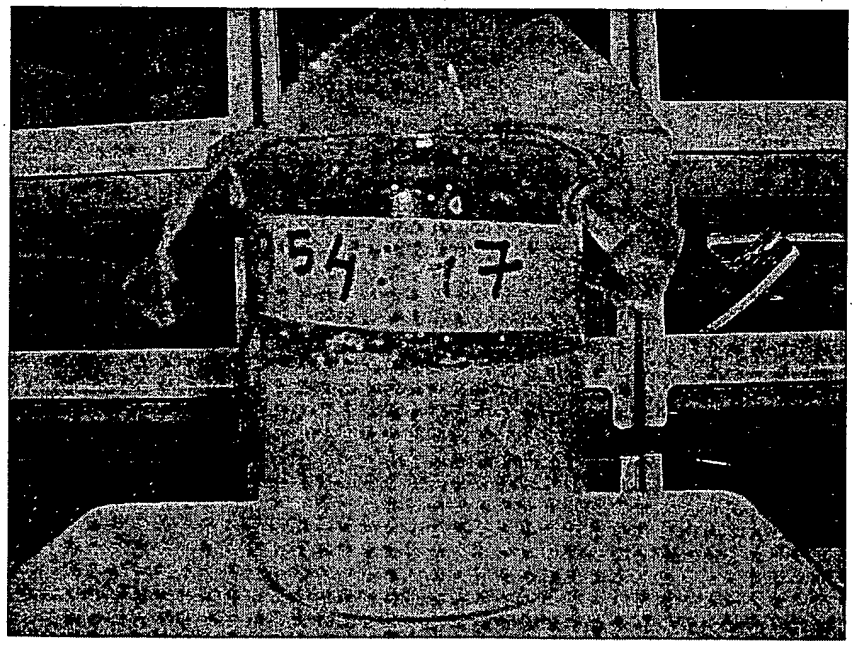
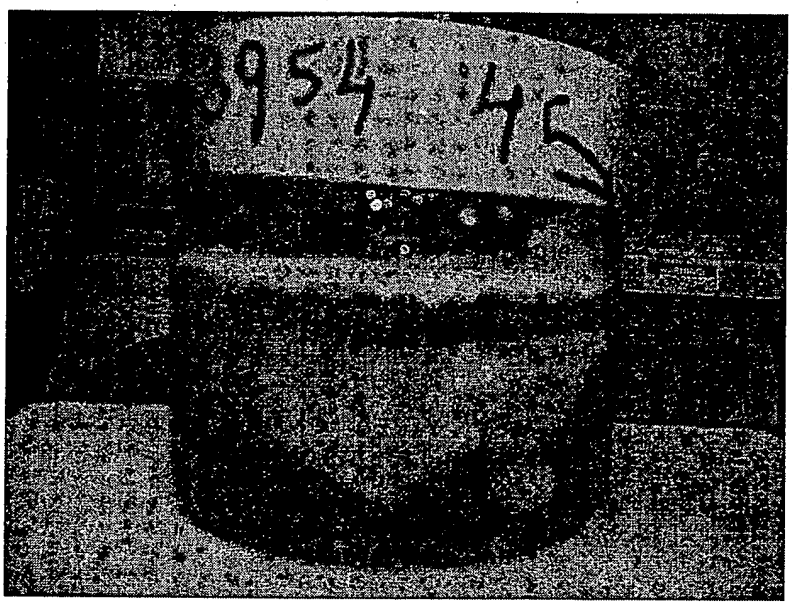


C2: 5 Equivalents Lauric Acid

Murthy Exhibits D1 and D2

Klink et al. – Lauric Acid (30% Tilmicosin; 41.4% Propylene Glycol)



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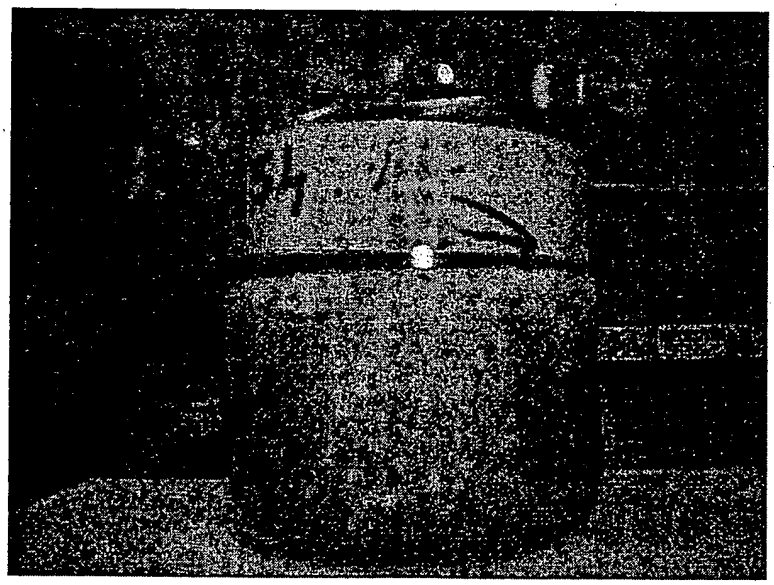
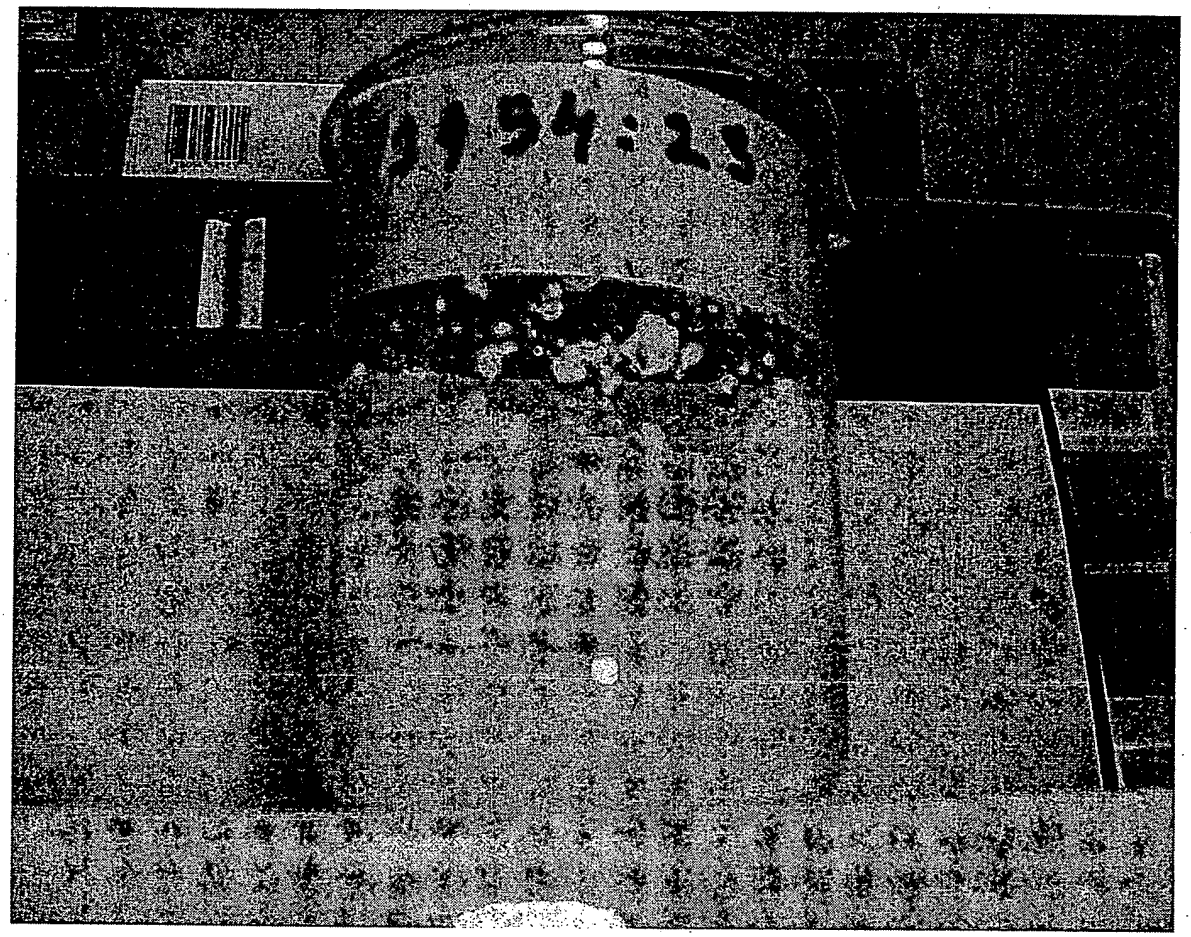


D2: 5 Equivalents Lauric Acid

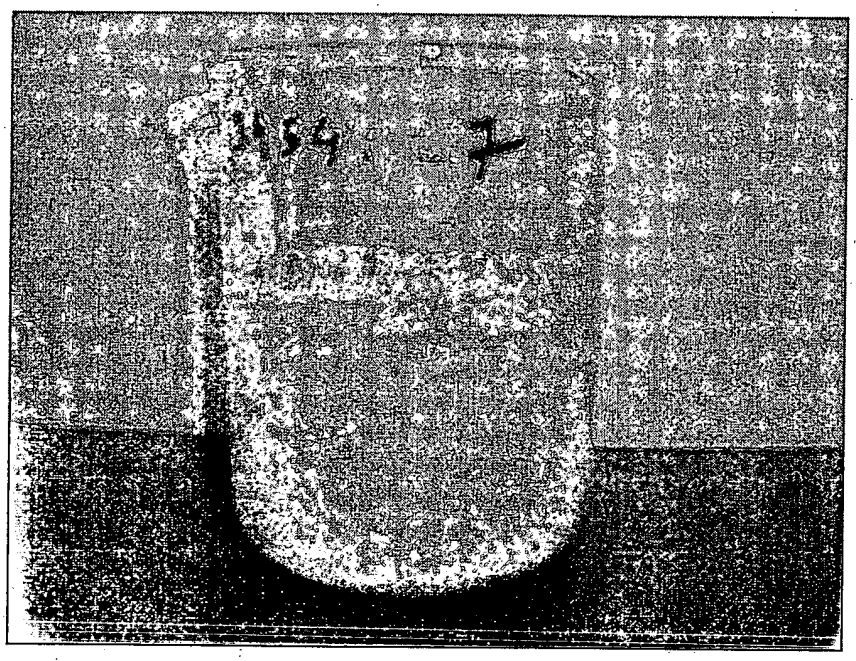
Murthy Exhibit E

Klink et al. – Palmitic Acid

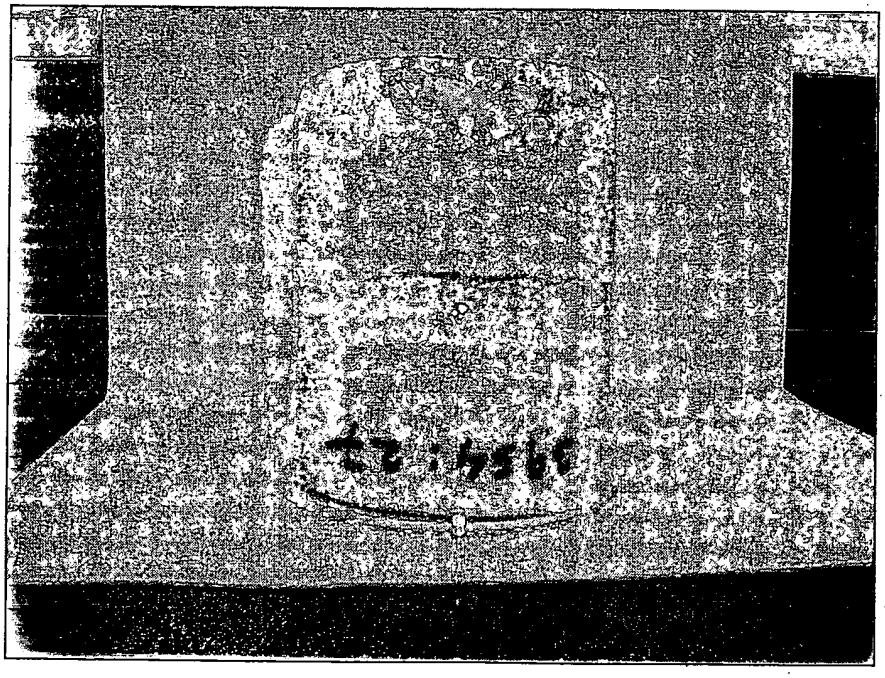


Murthy Exhibit F1 and F2

Klink et al. – Pamoic Acid



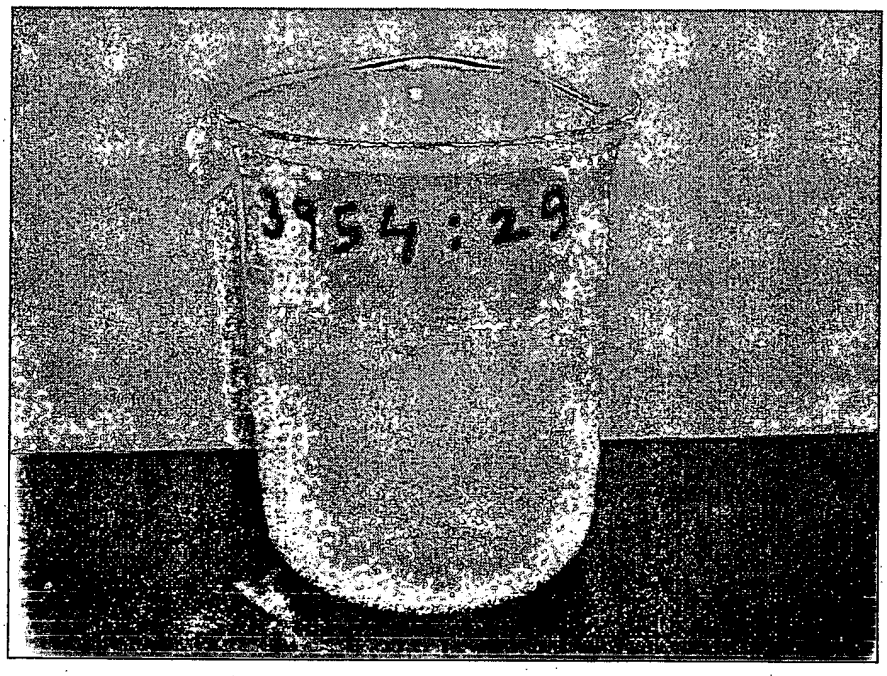
F1



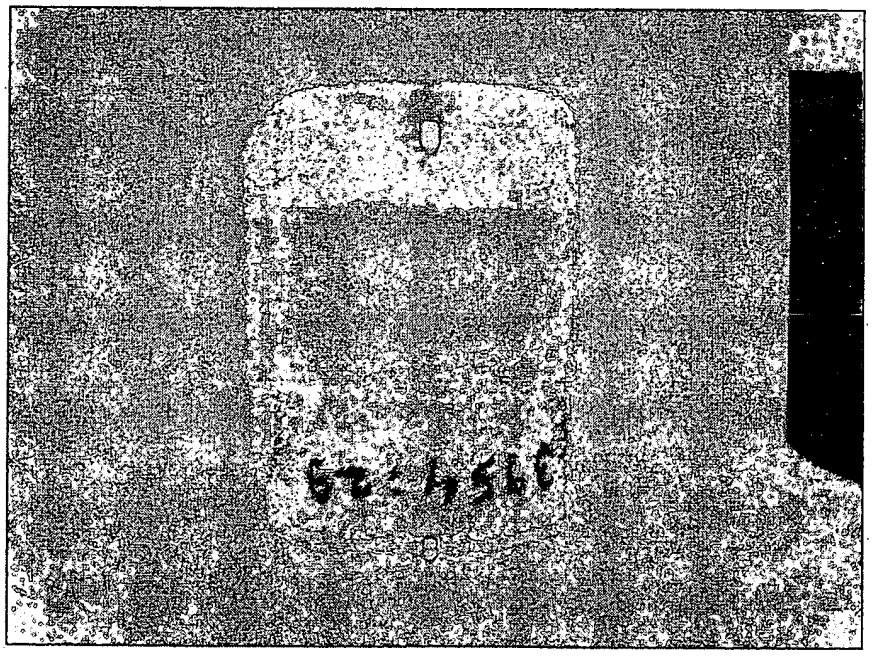
F2

Murthy Exhibit G1 and G2

Klink et al. – Stearic Acid



G1



G2

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10% Tilmicosin – Lauric Acid in 10% Propylene Glycol:90% Glycerol Formal (left)
3 ml of the 3954:75 formulation after injection into 50 ml water (right)